University Library

MINERVA ACCESS

A gateway to Melbourne's research publications

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
O'Mahony, EF;Hutchinson, DP;McGillivray, G;Nisbet, DL;Palma-Dias, R

Title:
Right-sided aortic arch in the age of microarray

Date:
2017-05-01

Citation:
O'Mahony, E. F., Hutchinson, D. P., McGillivray, G., Nisbet, D. L. & Palma-Dias, R. (2017). Right-sided aortic arch in the age of microarray. Prenatal Diagnosis, 37 (5), pp.440-445. https://doi.org/10.1002/pd.5029.

Persistent Link:
https://hdl.handle.net/11343/292636

Title: Right sided aortic arch in the age of microarray

Running Head: Right sided aortic arch in the age of microarray

Manuscript Word Count: 2532

Table Count 2

Figure Count 0

Authors: Edward F O'Mahony [1,2], Darren P Hutchinson[1,3], George McGillivray[1,4], Debbie L Nisbet[1], Ricardo Palma-Dias[1,2]

Institute:

1 Royal Women's Hospital, Parkville Victoria 3052

2 University of Melbourne, Victoria 3052

3 Royal Children's Hospital, Parkville, Victoria 3052

4 Victorian Clinical Genetics Services, Murdoch Children's Research Institute, Melbourne, Australia

Short title: Right sided aortic arch in the age of microarray

Corresponding Author:

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/pd.5029

This article is protected by copyright. All rights reserved.

Author Manuscript

Dr Edward O'Mahony,

Department of Ultrasound,

Pauline Gandel Women's Imaging Centre

Level 1, Royal Womens Hospital,

20 Flemington Road,

Parkville, VIC 3052

Phone 03-83452000

Fax 03-83452259

Email edward.omahony@thewomens.org.au

No external funding sources.

No Conflict of interest disclosures to be made.

This paper is not under simultaneous consideration elsewhere. There are no submissions and previous reports that might be regarded as redundant or duplicate publication of the same or very similar work. There are no financial and personal relationships between the authors and others that might bias our work.

Author Manuscript

This article is protected by copyright. All rights reserved.

What's already known about this topic?

Right sided aortic arch is a congenital vascular anomaly of the laterality of the aorta in relation to the trachea. Detection is clinically relevant for at least three reasons; coexistent intracardiac and extracardiac anomalies, possible postnatal vascular ring symptoms, and the potential for chromosomal anomalies including 22q11.2 deletion and trisomy 21. It is unknown whether microarray detects additional clinically relevant chromosome anomalies compared to standard karyotype and 6-probe FISH.

What does this study add?

- Microarray analysis identified clinically significant submicroscopic chromosomal anomalies not detectable by G-banded karyotype or 6-probe FISH (X,Y, 13, 18, 21, TUPLE).
- This is the first report of deletions at 9q31.2 and 6p21.31p21.2 in association with right aortic arch.
- The clinical implication of the chromosomal findings is that invasive testing with microarray analysis should be offered to patients when right sided aortic arch is diagnosed prenatally.

Author Manuscript

This article is protected by copyright. All rights reserved.

Key words:

Right-sided aortic arch, velocardiofacial, Di George, 22q11.2 deletion, ultrasound, SNP microarray.

Author Manuscript

This article is protected by copyright. All rights reserved.

Abstract

Objective: For fetuses with a diagnosis of right aortic arch and normal cardiac anatomy we aimed to establish the frequency of chromosomal anomaly diagnosed with SNP microarray analysis, particularly focusing on microduplications or microdeletions which would have gone undetected by conventional karyotyping and 6 probe fish (13,18,21, X,Y, TUPLE).

Method: Retrospective study of fetal ultrasounds between 2011 and 2016 in an Australian tertiary referral centre. Outcomes of interest were survival and postnatal surgery for vascular ring.

Results: 30 patients were identified, 24 were apparently isolated. Chromosomal anomalies were identified in 8 fetuses (32%) of 25 who had chromosomal testing. The rate in isolated cases was 11% and 56% in non-isolated cases. The 22q11.2 deletion was identified in three fetuses (12%). Microarray identified copy number variants of potential clinical significance In 4 additional fetuses (16%). Long continuous stretches of homozygosity were identified in one fetus with cerebellar hypoplasia potentially identifying the loci for recessive mutations. Surgery for vascular ring was performed on seven infants (25%)

Conclusion: Microarray detected clinically significant chromosomal anomalies in fetuses with right aortic arch that would not be detected with conventional karyotyping. Antenatal counselling should include the chance of postnatal surgery and the importance of longterm follow-up.

Author Manuscript

This article is protected by copyright. All rights reserved.

Author Manuscript

This article is protected by copyright. All rights reserved.

Introduction

Right sided aortic arch (RAA) is a congenital vascular anomaly of the laterality of the aorta in relation to the trachea due to abnormal regression of the embryonic aortic arches[1]. Prevalence is estimated at 0.05-0.1% [2, 3, 4]. There is evidence that detection rates are increasing with improved ultrasound equipment and operator training [4, 5]. Detection is clinically relevant for at least three reasons; coexistent intracardiac and extracardiac anomalies, possible postnatal vascular ring symptoms, and the potential for chromosomal anomalies. Whether antenatal microarray detects more chromosome anomalies than banded karyotype in the context of right sided aortic arch with normal cardiac anatomy is not known.

A RAA often accompanies other congenital cardiac defects, including tetralogy of Fallot, truncus arteriosus, atrial isomerism [5, 6]. Outcomes in studies on antenatally diagnosed right aortic arch which included mixed populations with major coexistent cardiac anomalies were determined by the major anomaly [5, 6, 7, 8]. For this reason, similar to the approach in some recent studies [4,9,10] we chose to focus exclusively on a study population with a RAA or double aortic arch (DAA) and normal or near-normal cardiac anatomy. In such populations, rates of extracardiac anomalies of 15-17% have been reported. [9]

Vascular rings are congenital anomalies of the aortic arch that result in compression of the tracheobronchial tree and/or oesophagus, leading to possible respiratory and gastrointestinal symptoms. Until recently reports of prenatal diagnosis of aortic arch

This article is protected by copyright. All rights reserved.

abnormalities were scarce. [11] Published reports were primarily observational case series of patients with vascular rings treated by surgical repair at tertiary centers [12-16]. DAA and RAA with an aberrant left subclavian artery (ALSA) and left ductus arteriosus or ligamentum form vascular rings. RAA with mirror-image branching are unlikely to cause compression upon the trachea or esophagus. Recent publications have reported high levels of successful antenatal ascertainment of branching patterns. [9, 17]

Commonly associated chromosomal anomalies with RAA include genetic or malformation syndromes such as DiGeorge syndrome (chromosome 22q11.2 deletion syndrome) [18] and Down syndrome (trisomy 21).

High resolution antenatal microarray technology has been routinely available in Victoria since 2012 and identifies submicroscopic copy number variations not detected on a conventional G-banded karyotype or 6 probe FISH. In addition to LogR 'copy number' data, single nucleotide polymorphism (SNP) arrays provide SNP genotyping data for estimating low levels of mosaicism, assessing long continuous stretches of homozygosity (LCSH) and the detection of uniparental disomy.

Our study hypothesis was that in an antenatally diagnosed population with a right sided aortic arch or double aortic arch with normal or near-normal cardiac anatomy, there will be additional chromosomal anomalies of clinical relevance detected which would have gone undetected by standard G-banded karyotyping and 6 probe FISH (13, 18, 21, X,Y, TUPLE). To

Author Manuscript

This article is protected by copyright. All rights reserved.

our knowledge, this study population represents the largest published with this antenatal diagnosis and microarray analysis.

Author Manuscript

This article is protected by copyright. All rights reserved.

Methods

A retrospective review of all fetal ultrasounds at our tertiary referral institution between 2011 and 2016 was performed. Fetuses with a RAA or DAA and normal or near normal intracardiac anatomy were included. Fetuses with a ventricular septal defect (VSD) were included, but atrio-ventricular septal defect and all other major intracardiac lesions were excluded. All fetuses underwent at least one fetal echocardiography study performed by a fetal cardiologist using either a Philips IU22, Epiq7 or GE Voluson E8 machine. The aortic arch and trachea were imaged in the standard 3 vessel and tracheal view in line with the ISUOG recommendations for fetal cardiac assessment. Axial thoracic views allowed assessment of aortic arch sidedness including relationship to trachea, ductal position, presence of aberrant vessels and assessment for double aortic arch. Colour flow, at slightly reduced Nyquist limit to usual (50 – 60 cm/s), was used in addition to 2D imaging with cephalad sweeps in the axial plane undertaken to determine aortic arch vessel branching patterns with improved assessment for aberrant subclavian vessels. Sagittal views were additionally obtained of the aortic and ductal arches, especially useful in assessment of double aortic arch. All women were counselled by a fetal cardiologist and a maternal fetal medicine specialist. Invasive testing was offered to all women with microarray molecular karyotyping available over the course of the study. Variables evaluated included nuchal translucency measurement, gestational age at diagnosis, identified extracardiac anomalies, additional intracardiac anomalies, aortic arch branching pattern, invasive testing, postnatal

Author Manuscript

This article is protected by copyright. All rights reserved.

chromosomal testing, postnatal imaging, additional postnatal diagnoses, postnatal symptoms and postnatal surgery on the aortic arch.

Copy number variants and LCSH were reviewed by a clinical geneticist. This study makes use of data generated by the DECIPHER community [19]. A full list of centres who contributed to the generation of the data is available from http://decipher.sanger.ac.uk and via email from decipher@sanger.ac.uk. Funding for the project was provided by the Wellcome Trust.

The study was approved by the hospital's ethics committee.

Results

Right aortic arch or DAA with normal or near normal anatomy was identified in 30 fetuses. This corresponds to 3.5% of all fetal cardiac examinations performed in this period in our unit. The number of cases detected per year was 5, 2, 5, 12, 6 respectively over the study period. The mean gestational age at diagnosis was 20 weeks. (Range 12-37 weeks). 24 were apparently isolated. Of the 25 fetuses with RAA, 15 had been referred with that diagnosis. Details of the individual cases are presented in Table 1.

Of 30 fetuses overall, double aortic arch was found in 5 (17%). Branching pattern was determined in 23 of 25 (92%) fetuses with RAA. ALSA was identified in 19 (76%) and mirror image branching in 4(16%). Of the three fetuses with 22q11.2, two had ALSA and the other had mirror image branching. There was a change in the postnatal branching pattern diagnosis in 7 cases, including three fetuses where the change was to DAA.

Author Manuscript

This article is protected by copyright. All rights reserved.

Nuchal Translucency

Nuchal translucency was measured in 20 cases, and was greater than the 95th percentile in 2 (10%) cases. The first of these (case 12) also had a small apical VSD. 22q11.2 deletion was found on microarray. The second (case 26) had a nuchal translucency of 8mm, and long continuous strands of homozygosity on microarray.

Associated extracardiac structural anomalies

In case 26, absent cavum septum pellucidum and ponto-cerebellar hypoplasia was suspected at 19 weeks gestation. On neurosonography there was absence of the cavum septum pellucidum on axial and coronal planes. On sagittal images, the cerebellar vermis was not visualised and the pons appeared thinned. Although the corpus callosum was not seen on ultrasound this was accepted as a normal ultrasound finding prior to 20 weeks. The antenatal suspicion was confirmed at postmortem which concluded that the corpus callosum was absent and the brain stem and cerebellum were markedly underdeveloped for gestation. A postnatal MRI was not performed. Two additional cases had soft marker findings, with a hypoplastic nasal bone (case 13) and choroid plexus cysts (case 8). Case 15 had a 22q11.2 deletion and had a postnatal finding of a soft palate cleft.

Associated intracardiac structural anomalies

There were 3 cases with a VSD (Case 12, Case 28 and Case 30). The VSDs were muscular in two cases and perimembranous in the third case. The 22q11.2 deletion was found in 2 of these fetuses.

Author Manuscript

This article is protected by copyright. All rights reserved.

Associated chromosomal anomalies

23 women elected to undergo invasive testing. Microarray was declined by 2 patients at the beginning of the study period, requesting only G-banded karyotyping and 6 probe FISH to eliminate the chance of copy number variants of uncertain significance. The remaining 21 women underwent chromosome microarray analysis. At the time of completion of the study, two further neonates had undergone postnatal testing. Of the 25 patients who underwent genetic testing prenatally or postnatally, 3 (12%) had the common recurring 22q11.21 deletion identified on microarray and one of these had RAA without an intracardiac anomaly. Copy number variations or LCSH not detectable by G-Banded karyotype or 6-probe FISH were identified in 5 cases (Table 2). The rate of a clinically significant chromosomal anomaly among fetuses where RAA or DAA was an apparently isolated finding on ultrasound was 11% (2 of 18 tested). In the presence of any additional structural anomaly the rate was 57% - (4 of 7 tested).

Outcome

Termination of pregnancy was requested by two women, (Case 12 and 26), both with a chromosomal anomaly and an associated intracardiac or extracardiac anomaly. All other babies were liveborn. Surgery for vascular ring was performed on seven infants (25%) who were liveborn, four with DAA. A further two infants underwent surgery for associated ventricular septal defect. No patients have been lost to follow up.

Author Manuscript

This article is protected by copyright. All rights reserved.

Author Manuscript

This article is protected by copyright. All rights reserved.

Discussion

This study has demonstrated that microarray analysis identified submicroscopic chromosomal anomalies or LCSH not detectable by G-banded karyotype or 6-probe FISH (X,Y, 13, 18, 21, TUPLE). This is the first report of deletions at 9q31.2 and 6p21.31p21.2 in association with right aortic arch. Determining the clinical significance of antenatally diagnosed and novel or unique copy number changes can be challenging and adds complexity to antenatal genetic counselling. In general terms, copy number changes inherited from phenotypically normal parents are more likely to be benign and de novo findings, particularly larger microdeletions are more likely to be clinically significant[20].

In case 13, a de novo 2.8Mb microdeletion likely to be pathogenic was identified at 9q31.2 in a fetus with an additional softmarker (hypoplastic nasal bone) and ocular ptosis diagnosed after birth. Two patients with smaller overlapping deletions listed in Decipher [19] had a VSD plus behavioural problems (Decipher case 274871) and hypoplasia of the corpus callosum, hypotonia and ptosis (Decipher case 261011), respectively. Case 25 had a 0.7Mb deletion at 6p21.31p21.2 inherited from the mother who has poor executive planning and decision-making skills. Case 26 had LCSH related to parental consanguinity. The fetus had a nuchal translucency of 8mm and an early diagnosis of right sided aortic arch at 12 weeks. Structural brain anomalies were suspected from 16 weeks and the pregnancy was terminated after persistence of these findings at 19 weeks. Cerebellar Hypoplasia was confirmed on post mortem. Assuming an underlying recessive aetiology for the anomalies

Author Manuscript

This article is protected by copyright. All rights reserved.

identified in this fetus, in the context of parental consanguinity, we reviewed the regions of homozygosity (LCSH) for candidate genes for future sequencing. Four genes were identified; namely POMGNT2 (congenital muscular dystrophy-dystroglycanopathy type A8), GMPPB (congenital muscular dystrophy-dystroglycanopathy type A14), PMPCA (cerebellar hypoplasia, non-progressive Norman type) and CHMP1A (pontocerebellar hypoplasia type 8).

In agreement with the recent systematic review in this field which reported a 14.1% chance of chromosomal anomaly [9], most fetuses in our RAA population had normal chromosomes and we found similar rates of 22q11.2 deletion. Our study population differs in its higher rates of invasive testing with availability of microarray karyotype technology, revealing a number of clinically significant copy number variations which would not have been detected by G-band karyotype or 6-probe FISH.

The finding that the rate of chromosomal anomaly is much higher among fetuses with RAA or DAA where an additional structural anomaly is detected on ultrasound may have clinical implications when counselling patients who are reluctant to undergo invasive testing. This also reinforces the importance of an expert anomaly scan and fetal echocardiography when a RAA is detected to exclude associated anomalies.

Ours is a highly selected study population with exclusion of coexistent major intracardiac anomalies which has some implications to consider when comparing our results to other studies in this field. Fetuses with a right sided aortic arch and a coexistent intracardiac

Author Manuscript

This article is protected by copyright. All rights reserved.

anomaly have very high rates of mirror image branching [6]. Chromosomal anomalies detected in fetuses with RAA using G-banded karyotype and 6-probe FISH are more common when there are intracardiac anomalies.[7] Our study population could be expected to demonstrate lower rates of mirror image branching and chromosomal anomalies detected by traditional methods and a high proportion of fetuses with aberrant vessels. It is known that children with aberrant subclavian vessels have increased rates of chromosomal anomalies [21] including some submicroscopic chromosomal anomalies which could only be detected by microarray[22]. The association of submicroscopic chromosomal anomalies may differ in selected study populations such as ours, and our novel findings support this. This merits further examination in the future to facilitate lesion-specific counselling and management for right sided aortic arch.

The decision by two patients early in the study period to decline microarray in favour of karyotype and 6 probe FISH probably reflects a level of clinician and patient discomfort with management of copy number changes of uncertain significance, which declined over the course of the study as clinician familiarity with the technology and management of results increased.

Similar to other recent studies we report high rates of determination of branching pattern of head and neck vessels. [9,17]As reported elsewhere[10] the differential diagnosis of a double aortic arch and a right sided aortic arch can be challenging. Postnatal change of diagnosis to

This article is protected by copyright. All rights reserved.

double aortic arch was seen in three cases in our study population. Assessment of the aortic arch should always include sagittal views to add additional information to the axial plane alone, including further information of vessel calibre. In double aortic arch two separate aortic arches will be seen either side of the fetal trachea by slow back and forth sweeping. Relative sizes of each arch can be appreciated, with the right arch generally being dominant. Sagittal views can easily be obtained by rotating 90 degrees on the aortic arch seen in the axial view or additionally by use of transducers allowing simultaneous biplane views. Newer modalities such as STIC (+/- colour flow) and B-Flow can also be used to give a 3D representation of the anatomy.

The main limitations of the study are that it is retrospective with a small population due to the rarity of the condition and the fact that microarray technology has only relatively recently become clinically available. Our study does not inform the long term outcome in children with RAA that most parents will desire when being counselled with this antenatal finding.

Long term follow-up will provide a basis to collect information for improved antenatal counselling of parents faced with this diagnosis. Clarity of the clinical significance of copy number variations identified in this study should increase over time as genetics databases gain information about more patients with antenatal diagnosis of fetal RAA. For this reason ongoing audit of the microarray results in this condition is recommended and a statewide,

Author Manuscript

This article is protected by copyright. All rights reserved.

national or international clinical registry of antenatally diagnosed fetal cardiovascular anomalies is a consideration.

Conclusion

We believe the clinical implication of the chromosomal findings in this study is that invasive testing with microarray analysis should be offered to patients when fetal RAA is diagnosed antenatally. We expect that the rate of chromosomal anomaly will be higher among fetuses where an additional structural anomaly is detected on ultrasound. Consent for invasive testing needs to include information about the chance of identifying a copy number change of uncertain significance that may result in parental anxiety. Parents also need to be forewarned about the need for and risk of surgery in infancy, particularly where a double aortic arch is identified. It is important to explain the need for neonatal follow up in the short term to exclude double aortic arch with postnatal imaging and in the medium to longer term for symptoms of vascular ring.

References

1 Knight L, Edwards JE Right Aortic Arch - Types and Associated Cardiac Anomalies, Circulation 50, 1974 Pg 1047

Author Manuscript

This article is protected by copyright. All rights reserved.

2 Hastreiter AR, D'Cruz IA, Cantez T et al. Right-sided aorta. I. Occurrence of right aortic arch in various types of congenital heart disease. II. Right aortic arch, right descending aorta, and associated anomalies. Br Heart J 1966; 28: 722-739.

3 Achiron R, Rotstein Z, Heggesh J et al. Anomalies of the fetal aortic arch: a novel sonographic approach to in-utero diagnosis. Ultrasound Obstet Gynecol 2002; 20: 553-557.

4 Mogra R, Kesby G, Sholler G et al. Identification and management of fetal isolated right sided aortic arch in an unselected population. Ultrasound Obstet Gynecol. 2016 Feb 26. doi: 10.1002/uog.15892. [Epub ahead of print]

5 Zidere V, Tsapakis EG, Huggon IC et al. Right aortic arch in the fetus. Ultrasound Obstet Gynecol 2006; 28: 876-881.

6 Berg C, Bender F, Soukup M et al. Right aortic arch detected in fetal life. Ultrasound Obstet Gynecol 2006; 28: 882-889

7 Miranda JO, Callaghan N, Miller O et al. Right aortic arch diagnosed antenatally: associations and outcome in 98 fetuses. Heart 2014; 100: 54-59.

8 Li S, Luo G, Norwitz ER et al. Prenatal diagnosis of congenital vascular rings and slings: sonographic features and perinatal outcome in 81 consecutive cases. Prenat Diagn 2011; 31: 334-346.

9 F D'Antonio, A Khalil, V Zidere et al. Fetuses with right aortic arch Multicentre cohort study and meta-analysis. 10.1002/uog.15805

Author Manuscript

This article is protected by copyright. All rights reserved.

10 Razon Y, Berant M, Fogelman R et al. Prenatal diagnosis and outcome of right aortic arch without significant intracardiac anomaly. J Am Soc Echocardiogr 2014; 27: 1352- 1358.

11 Yoo SJ, Min JY, Lee YH et al. Fetal sonographic diagnosis of aortic arch anomalies. Ultrasound Obstet Gynecol. 2003;22(5):535.

12 Shah RK, Mora BN, Bacha E, et al. The presentation and management of vascular rings: an otolaryngology perspective. Int J Pediatr Otorhinolaryngol 2007; 71:57.

13 Humphrey C, Duncan K, Fletcher S. Decade of experience with vascular rings at a single institution. Pediatrics 2006; 117:e903.

14 Woods RK, Sharp RJ, Holcomb GW 3rd, et al. Vascular anomalies and tracheoesophageal compression: a single institution's 25-year experience. Ann Thorac Surg 2001; 72:434.

15 Backer CL, Mavroudis C, Rigsby CK et al. Trends in vascular ring surgery. J Thorac Cardiovasc Surg 2005; 129:1339.

16 Turner A, Gavel G, Coutts J. Vascular rings--presentation, investigation and outcome. Eur J Pediatr 2005; 164:266.

17 Galindo A, Nieto O, Nieto MT et al. Prenatal diagnosis of right aortic arch: associated findings, pregnancy outcome, and clinical significance of vascular rings. Prenat Diagn 2009; 29: 975-981.

Author Manuscript

This article is protected by copyright. All rights reserved.

18 McElhinney DB, McDonald-McGinn D, Zackai EH et al. Cardiovascular anomalies in patients diagnosed with a chromosome 22q11 deletion beyond 6 months of age. Pediatrics 2001; 108:E104.

19 DECIPHER: Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources. Firth, H.V. et al (2009). Am.J.Hum.Genet 84, 524-533 (DOI:dx.doi.org/10/1016/j.ajhg.2009.03.010)

20 de Vries BB, Pfundt R, Leisink M et al. Diagnostic genome profiling in mental retardation. Am. J. Hum. Genet. 2005;77:606–16

21 Borenstein M, Cavoretto P, Allan L et al. Aberrant right subclavian artery at 11 + 0 to 13 + 6 weeks of gestation in chromosomally normal and abnormal fetuses. Ultrasound Obstet Gynecol 2008; 31: 20–24.

22 Rembouskos G, Passamonti U, De Robertis V et al. Aberrant right subclavian artery (ARSA) in unselected population at first and second trimester ultrasonography. Prenat Diagn 2012; 32: 968–975.

Author Manuscript

This article is protected by copyright. All rights reserved.

Tables and Figures

Table 1

Case Summary table

Case No.	Gest Diag (Wk)	Referral Reason	Fetal Echo findings	Branch Pattern	Additional Antenatal findings	Ductus	Outcome	ChangedPostnatalecho	Additional Postnatal findings	Surgery	Age (Yr)
1	22	RAA	RAA	ALSA	N	L	Livebirth	N	N	N	4.7
2	20	RAA	RAA	ALSA	N	L	Livebirth	N	N	N	4
3	20	Routine	RAA	ALSA	N	L	Livebirth	N	N	N	4.5
4	20	RAA	RAA	Unknown	N	L	Livebirth	ALSA	N	N	4
5	20	RAA	RAA	ALSA	N	L	Livebirth	N	N	N	3.6
6	20	RAA	RAA	MI	N	L	Livebirth	DAA	N	Y	3.4
7	27	RAA	RAA	MI	Del 17p11.2	L	Livebirth	N	N	N	2.8
8	12	RAA	RAA	ALSA	Choroid plexus cysts	L	Livebirth	N	N	N	2.4

Author Manuscript

This article is protected by copyright. All rights reserved.

9	20	RAA	RAA	ALSA	N	L	Livebirth	DAA	N	N	1.4
10	17	RAA	RAA	ALSA	N	L	Livebirth	N	N	Y	1.8
11	17	Routine	RAA	ALSA	N	L	Livebirth	N	N	N	1.1
12	20	RAA	RAA	MI	VSD 22q11.2 Del	L	ToP				
13	20	Routine	RAA	Unknown	Hypoplastic nasal bone Del 9q31.2	L	Livebirth	ALSA	Left eye ptosis	N	1.6
14	32	APH	RAA	Unknown	N	L	Livebirth	N	N	N	1.8
15	20	RAA	RAA	ALSA	22q11.2 Del	L	Livebirth	N	Soft palate cleft	Y	1.5
16	19	RAA	RAA	MI	N	L	Livebirth	N	N	N	1.4
17	20	Routine	RAA	MI	N	R	Livebirth	N	N	N	1.3
18	23	RAA	RAA	ALSA	Dup. 9p21.2	L	Livebirth	N	N	N	1.4
19	20	RAA	RAA	ALSA	N	L	Livebirth	N	N	N	1.1
20	20	RAA	RAA	MI	N	L	Livebirth	ALSA	N	N	1.1
21	20	Routine	RAA	ALSA	N	L	Livebirth	N	N	N	0.8

Author Manuscript

This article is protected by copyright. All rights reserved.

22	21	Routine	RAA	ALSA	N	L	Livebirth	N	N	Y	0.8
23	20	DAA	LAA	Unknown	N	L	Livebirth	DAA	N	Y	3.1
24	19	DAA	DAA	DAA	N	L	Livebirth	N	N	Y	1
25	26	Abnormal 3 Vessel view	RAA	Unknown	Deletion 6p21.31p21.2	L	Livebirth	ALSA	N	N	0.7
26	12	9mm NT	RAA	Unknown	LCSH. SUA absent CSP, CC, cerebellar hypoplasia	L	ToP				
27	20	Routine	RAA	MI	N	L	Livebirth	ALSA	N	N	0.4
28	20	Routine	RAA	ALSA	VSD Ascites	L	Livebirth	N	N	Y For VSD	0.3
29	20	Routine	DAA	DAA	N	L	Livebirth	N	N	Y	0.2
30	37	Growth Scan	RAA	ALSA	VSD 22q11.2 Del	L	Livebirth	N	N	Y For VSD	0.4

Author Manuscript

This article is protected by copyright. All rights reserved.

Key: Del – Deletion. ALSA – Aberrant left subclavian artery. APH – antepartum haemorrhage. CC – corpus callosum. CSP – cavum septum pellucidum. DAA – double aortic arch. Dup – duplication. Del – deletion. LCSH – long continuous strands of homozygosity. L – left. LTF – loss to follow-up. MI – mirror image branching. N – no. NT – nuchal translucency. R- right. SUA – single umbilical artery. VSD – ventricular septal defect. Y = yes.

Author Manuscript

This article is protected by copyright. All rights reserved.

Table 2

Abnormalities on chromosome microarray analysis.

Author Manuscript

Case	Chromosomal Anomaly [GRCh37/hg19 co-ordinates]	Detectable by G-band karyotype/ FISH?	Inheritance	Cardiac	Extracardiac	Clinical Significance	Outcome
12	2.6 Mb deletion 22q.11.21 [21:18,877,787-21,462,353]	Y	De Novo	VSD		Pathogenic	ToP
15	2.6 Mb deletion 22q.11.21 [21:18,877,787-21,462,353]	Y	-	-	Postnatal soft palate cleft	Pathogenic	Livebirth
30	2.6 Mb deletion 22q.11.21 21[18,892,575-21,480,220]	Y	De Novo	VSD		Pathogenic	Livebirth
13	2.8 Mb deletion 9q31.2	N	De Novo	-	Hypoplastic nasal	Uncertain,	Livebirth

This article is protected by copyright. All rights reserved.

	[9:108,350,181-111,123,697]				bone Left eye ptosis	Likely Pathogenic	
25	0.73 Mb deletion 6p21.31p21.2 [6:36,098,410-36,831,569]	N	Maternal	-		Uncertain, likely pathogenic	Livebirth
26	Long continuous stretches of homozygosity (>2Mb) on chromosomes 1,2,3,4,7,9, 10,11,13,16,17,19,20,21 *Candidate genes [homozygosity]* *POMGNT2 [3:16258891-45157568]* *GMPPB [3:46600520-77133873]* *PMPCA [9:137909610-141044489]* *CHMP1A [16:86345298-*	N	Consanguinous 1st cousin	-	Single umbilical artery absent CSP, CC cerebellar hypoplasia	Loci for candidate recessive genes	ToP

Author Manuscript

This article is protected by copyright. All rights reserved.

	90148796]						
7	0.42 MB Deletion in 17p11.2 [17:18,505,769-18,922,171]	N	Maternal	-	-	Uncertain, likely benign	Livebirth
5	0.55 MB Duplication. 9p21.2 [9:27,430,232-27,980,402]	N	Paternal	-	-	Uncertain, likely benign	Livebirth

Author Manuscript

This article is protected by copyright. All rights reserved.